Journal of Surgical Oncology 1998;69:162–167

Does Gross Appearance Indicate Prognosis in Intrahepatic Cholangiocarcinoma?

MASAKAZU YAMAMOTO, MD,[1]* KEN TAKASAKI, MD,[1] TATSUYA YOSHIKAWA, MD,[1] KEIKO UENO, MD,[2] AND MASAYUKI NAKANO, MD[3]

[1]*Department of Gastrointestinal Surgery, Institute of Gastroenterology, Tokyo Women's Medical College, Tokyo, Japan*

[2]*Division of Radiology, Tokyo Women's Medical College, Tokyo, Japan*

[3]*Division of Pathology, Chiba University Hospital, Chiba, Japan*

Background and Objectives: Survival after surgery for intrahepatic cholangiocarcinoma (ICC) is usually poor. The objective of this study was to investigate whether the gross appearance of ICC indicates postoperative prognosis.

Methods: Seventy patients with ICC underwent hepatectomy, with a 50% curative resection rate. Tumors were classified according to gross appearance [mass-forming (n = 28), periductal-infiltrating (n = 14), intraductal growth (n = 10), and mass-forming plus periductal-infiltrating (n = 18)], and the presence of lymph node or intrahepatic metastasis was studied microscopically.

Results: The incidence of positive lymph nodes was significantly higher in the patients with mass-forming plus periductal-infiltrating tumors than in those with intraductal growth tumors ($P = 0.0089$). The curative resection rate was significantly lower in patients with mass-forming plus periductal-infiltrating tumors than in those with either mass-forming or intraductal growth tumors ($P = 0.0001$, $P = 0.0048$, respectively). The 5-year survival rate after surgery in patients with mass-forming plus periductal-infiltrating tumors (0%) was significantly lower than that in patients with mass-forming tumors (39%) or intraductal growth tumors (69%) ($P = 0.0036$, $P = 0.0011$, respectively). Multivariate analysis using Cox's hazards model revealed that lymph node metastasis ($P = 0.0109$) and curative resection ($P = 0.0315$) were statistically significant independent prognostic factors; however, macroscopic types were not.

Conclusions: Patients with mass-forming plus periductal-infiltrating ICCs have a poor prognosis; however, the macroscopic types may not be a statistically significant independent prognostic factor.

J. Surg. Oncol. 1998;69:162–167.

KEY WORDS: **intrahepatic cholangiocarcinoma; gross appearance; postoperative survival**

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is a rare tumor associated with poor survival after resection. Because most cases of ICC are detected at an advanced stage, curative resection is often impossible. Although patients have survived for more than 5 years after surgery [1–4], survival rates after surgery have not yet been reported for a large series of patients treated at a single institution [5,6]. Over the past two decades, we have performed hepatic resection in more than 1,200 patients with primary hepatic carcinoma, including 83 with ICC. Morphologic features and metastasis have been studied in

*Correspondence to: Masakazu Yamamoto, MD, Tokyo Metropolitan Ebara Hospital, 4-5-10, Higashi-Yukigaya Ohta-ku, Tokyo, 145-0065 Japan. Fax No.: (81)3-5734-8023.

Accepted 22 September 1998

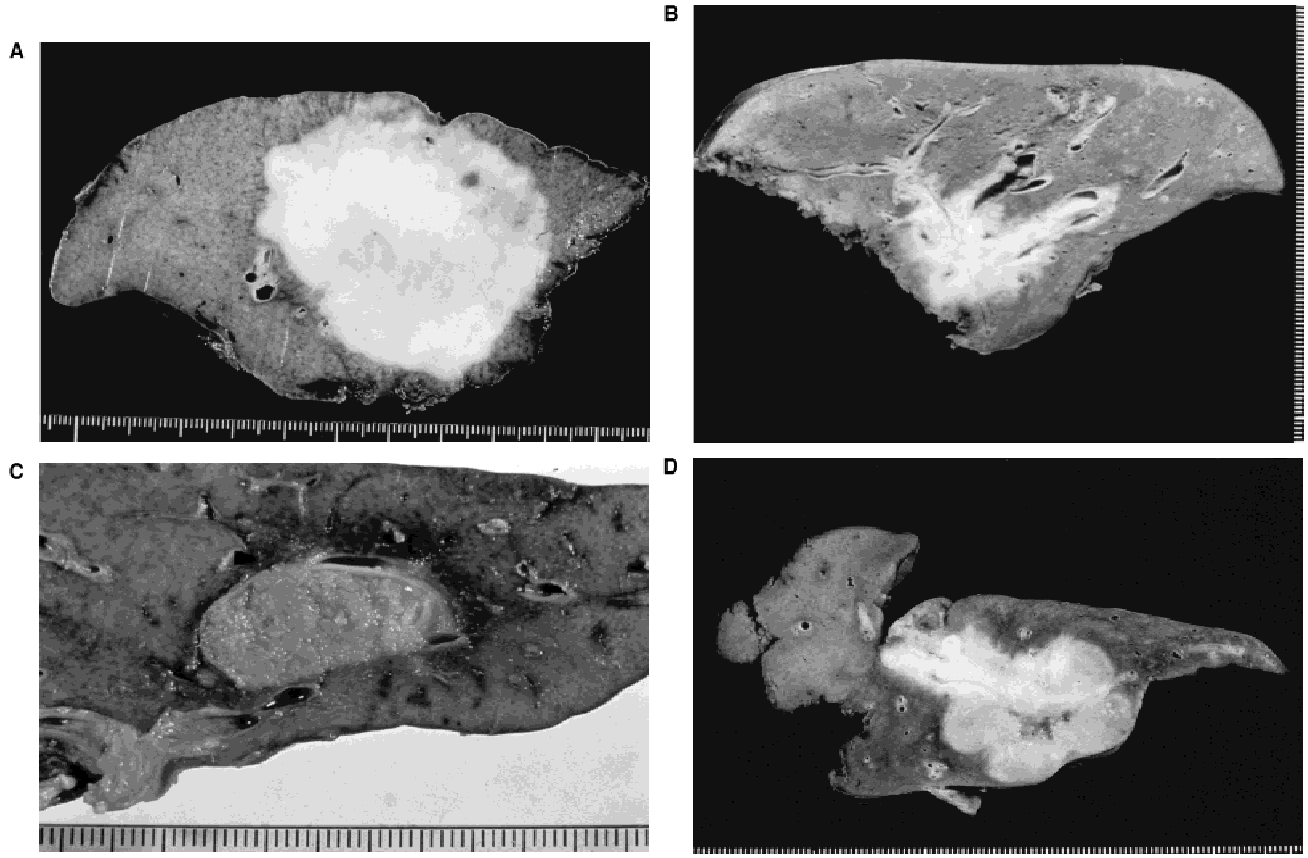

Fig. 1. Gross appearance of intrahepatic cholangiocarcinoma (maximum diameter). **A:** Mass-forming type (5.7 cm). **B:** Periductal-infiltrating type (3.5 cm). **C:** Intraductal growth type (2.5 cm). **D:** Mass-forming plus periductal-infiltrating type (4.5 cm).

detail. The aim of this study was to determine whether macroscopic features indicate prognosis after surgery.

MATERIALS AND METHODS

Eighty-three patients with ICC underwent surgical resection from November 27, 1980, through February, 15, 1996, at the Institute of Gastroenterology, Tokyo Women's Medical College, Tokyo. Cases of hilar cholangiocarcinoma were excluded. Peritoneal dissemination was also present in five patients. Intrahepatic metastases were present in the residual liver in eight patients. These 13 patients were excluded from the study. The remaining 70 patients were studied. Patients did not receive any chemotherapy during the preoperative or postoperative period.

ICCs were classified on the basis of gross appearance—mass-forming, periductal-infiltrating, intraductal growth, or mass-forming plus periductal-infiltrating types—as proposed by the Liver Cancer Study Group of Japan [7]. Mass-forming tumors (n = 28) are characterized by the presence of a nodular mass in the liver parenchyma, with a distinct border (Fig. 1A). Periductal-infiltrating tumors (n = 14) are characterized by tumor infiltration along the bile duct; they occasionally involve the surrounding blood vessels or hepatic parenchyma (Fig. 1B). Intraductal growth tumors (n = 10) are characterized by papillary growth or granular growth or both within the bile duct lumen (Fig. 1C). Mass-forming plus periductal-infiltrating tumors (n = 18) have both mass-forming and periductal-infiltrating features (Fig. 1D).

Lymph node metastasis and intrahepatic metastasis were also noted and confirmed histopathologically.

Cumulative survival rates of all patients were calculated with the Kaplan-Meier method; survival rates were compared using the log-rank test. The duration of survival was defined as the time from the first liver surgery to the date of death or last contact. For comparisons between the macroscopic subgroups, the chi squared test was used. Several clinicopathologic factors, including those found to be associated with patient survival by univariate analysis, were subjected to multivariate analysis using Cox's proportional hazards model. The significance level was set at $P < 0.05$.

RESULTS

Characteristics of Patients

Of the 70 patients in this study, 43 were men and 27 were women, with a mean age of 59.9 years (range 30 to

TABLE I. Relation Between Gross Appearance of Intrahepatic Cholangiocarcinoma and Patient Characteristics and Presenting Symptoms

Characteristics	Mass-forming (n = 28)	Periductal-infiltrating (n = 14)	Intraductal growth (n = 10)	Mass-forming + periductal-infiltrating (n = 18)	Total (n = 70)
Sex					
Male	17	8	8	10	43
Female	11	6	2	8	27
Mean age, years (range)	60.9 (30–74)	60.2 (37–79)	62.2 (40–74)	61.1 (32–74)	59.9 (30–79)
Jaundice	1	6*	1	11**	19
Pain	3	3	5***	8***	19
Fever	0	3	6**	4	13

*$P = 0.0013$ vs. mass-forming.
**$P < 0.0001$ vs. mass-forming.
***$P = 0.0089$ vs. mass-forming.

79 years). Sex and age did not differ significantly among patients in different subgroups of macroscopic appearance of ICC. Jaundice was the most common symptom in patients with periductal-infiltrating or mass-forming plus periductal-infiltrating tumors, whereas fever was the most common symptom in patients with intraductal growth tumors (Table I).

Surgical Procedures

Hepatic lobectomy was performed in 57 of the 70 patients, and resection of the biliary confluence was performed in 44. Lymph node dissection was performed at the hepatoduodenal ligament and surrounding the common hepatic artery in 51 patients (Table II). Two of the 70 patients (one with periductal-infiltrating tumor and one with mass-forming plus periductal-infiltrating tumor) died within 30 days after surgery (mortality rate 3%).

Curative resection was performed in 35 of the 70 patients (50%). The curative resection rate was significantly lower in patients with mass-forming plus periductal-infiltrating tumors than in those with either mass-forming or intraductal growth tumors ($P = 0.0001$, $P = 0.0048$, respectively) (Table II). Among the 18 patients with mass-forming plus periductal-infiltrating tumors, curative resection was precluded by cancer at the stump of the contralateral hepatic bile duct in 12 patients and by cancer at the major vessels at the hepatic hilum in six patients.

Lymph Node Metastasis and Intrahepatic Metastasis

Lymph node metastasis and intrahepatic metastasis were observed, respectively, in two and one of 10 patients with intraductal growth tumors compared with 11 and six of 18 patients with mass-forming plus periductal-infiltrating tumors. The rate (11/15) of lymph node metastasis (positive/dissected) in patients with mass-forming plus periductal-infiltrating tumors was significantly higher ($P = 0.0089$) than that (2/10) in patients with intraductal growth tumors (Table II).

Long-Term Outcome of Surgery

The 5-year survival rate after curative resection (53%) was significantly higher ($P < 0.0001$) than that after palliative resection (4%). The 5-year survival rates of patients with intraductal growth tumors (69%) or with mass-forming tumors (39%) were significantly better than that of patients with mass-forming plus periductal-infiltrating tumors (0%) ($P = 0.0011$, 0.0036). (Fig. 2).

Univariate analysis revealed that jaundice ($P = 0.0002$), lymph node metastasis ($P < 0.0001$), and curative resection ($P < 0.0001$) were statistically significant risk factors influencing prognosis in patients with ICCs (Table III). Multivariate analysis was performed with the following factors as covariables: jaundice, macroscopic type, lymph node metastasis, liver metastasis, and curative resection.

Of these, lymph node metastasis ($P = 0.0109$) and curative resection ($P = 0.0315$) were found to be statistically significant independent risk factors; however, macroscopic type was not (Table IV).

DISCUSSION

Curative surgical resection in cases of cholangiocarcinoma significantly increases survival and provides the only chance of cure. Reported rates of curative resection have varied from 10% to 91%, and 5-year survival rates have varied from 10% to 44% [6,8–10]. These reports included all sites of cholangiocarcinoma, and most reports excluded ICC from analysis or had small numbers of cases of ICC. Recently, because major hepatic resection has become safer and imaging for hepatic tumors has improved markedly, hepatic resection has been performed more frequently for ICC. The 5-year survival rate

TABLE II. Relation Between Gross Appearance of Intrahepatic Cholangiocarcinoma and Surgical Procedures and Characteristics of Metastasis

Resection type and metastasis	Mass-forming (n = 28)	Periductal-infiltrating (n = 14)	Intraductal growth (n = 10)	Mass-forming + periductal-infiltrating (n = 18)	Total (n = 70)
Hepatic lobectomy	17	13	10	17	57
Resection of biliary confluence and/or extrahepatic bile duct	11	11*	8	14**	44
Curative resection	21	4***	7	3****	35
Lymph node metastasis (positive/dissected)	6/14	4/12	2/10	11/15*****	23/51
Intrahepatic metastasis	4	0	1	6	11

*P = 0.0163 mass-forming.
**P = 0.0105 mass-forming.
***P = 0.0039 vs. mass-forming.
****P = 0.0001 vs. mass-forming; P = 0.0048 vs. intraductal growth.
*****P = 0.0089 vs. intraductal growth.

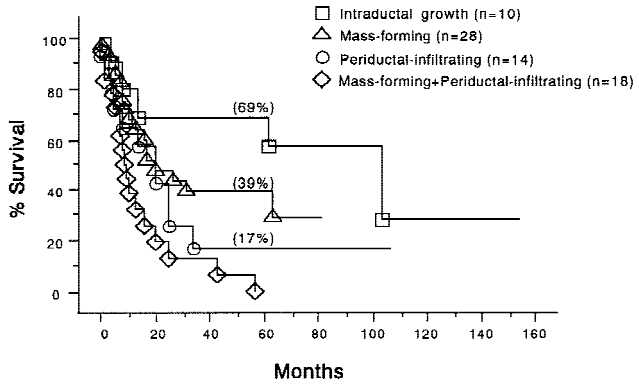

Fig. 2. Cumulative survival curve after surgery for intrahepatic cholangiocarcinoma. Long-term survival after surgery in cases of intraductal growth type or mass-forming type (P = 0.0011, P = 0.0036) was significantly better than that in cases of mass-forming plus periductal-infiltrating type.

after curative resection for ICC in our series was 53%. Because ICC is not considered an incurable tumor, it is important to determine whether curative resection can be performed.

Several factors, including negative microscopic margins, positive hilar lymph nodes, preoperative serum albumin and total bilirubin concentrations, performance status, and tumor grade, have been suggested to be prognostic factors in cholangiocarcinoma [5,6,8–11]. However, macroscopic type was not mentioned in these reports. Yasui et al. [12] reported that a new macroscopic classification can predict outcome in patients with liver metastases from colorectal cancer. They showed that macroscopic type reflects the biologic behavior of the metastatic lesion. Therefore, the present study investigated whether the gross appearance of ICC correlates with outcome after surgery.

A commonly used morphologic classification proposed by Weinbren and Mutum [13] divides extrahepatic cholangiocarcinoma into nodular, sclerosing, and papillary types. Patterns of tumor spread in patients with cholangiocarcinoma were studied by Weinbren and Mutum [13] and by Nakajima et al. [14], who suggested that the characteristics of invasion were influenced by the site of origin. Periductal-infiltrating tumors originating from major ducts near the hilum are often associated with interstitial infiltration or lymph duct involvement in the portal area. In contrast, mass-forming tumors originating from a small, peripheral bile duct sometimes directly invade the adjacent liver parenchyma through the sinusoid with minimal portal area invasion. These growth patterns are reflected by clinical symptoms. Periductal-infiltrating or mass-forming plus periductal-infiltrating ICCs infiltrate the porta hepatis, causing obstructive jaundice. At this stage, the tumor is already associated with massive invasion of the hepatoduodenal soft tissue or major vessels at the porta hepatis, precluding curative resection. The clinical characteristics of periductal-infiltrating tumors are considered to be similar to those of hilar cholangiocarcinomas, but ICCs with obstructive jaundice are detected at a more advanced stage than are hilar cholangiocarcinomas.

Univariate analysis revealed that patients with mass-forming plus periductal-infiltrating ICCs had significantly poorer outcomes after hepatectomy than did patients with mass-forming or intraductal growth ICCs. The analysis showed that mass-forming plus periductal-infiltrating ICCs had a high percentage of lymph node metastasis and that patients with these tumors had not undergone curative resection. Therefore, the macroscopic types of ICC must be recognized and differentiated with imaging studies before surgery.

Recent improvements in imaging techniques have allowed liver tumors to be more accurately visualized. Im-

TABLE III. Univariate Analysis of Prognostic Factors of Intrahepatic Cholangiocarcinoma

Variable	Hazard ratio	95% Confidence limits		*P* value
		Lower	Upper	
Jaundice				
Negative	1			
Positive	3.106	1.721	5.606	0.0002
Macroscopic types				
Mass-forming + periductal-infiltrating	1			
Mass-forming	0.383	0.193	0.761	0.0061
Periductal-infiltrating	0.547	0.252	1.187	0.1269
Intraductal growth	0.209	0.073	0.596	0.0034
Lymph node metastasis				
Negative	1			
Positive	4.688	2.170	10.126	<0.0001
Intrahepatic metastasis				
Negative	1			
Positive	2.009	0.955	4.223	0.0658
Resection				
Noncurative	1			
Curative	0.249	0.135	0.458	<0.0001

TABLE IV. Multivariate Analysis of Prognostic Factors of Intrahepatic Cholangiocarcinoma

Variable	Hazard ratio	95% Confidence limits		*P* value
		Lower	Upper	
Jaundice	1.514	0.603	3.802	0.3773
Macroscopic types				
Mass-forming	0.590	0.181	1.918	0.3799
Periductal-infiltrating	0.723	0.270	1.934	0.5187
Intraductal growth	0.565	0.155	2.064	0.3876
Lymph node metastasis	3.277	1.314	8.175	0.0109
Intrahepatic metastasis	1.612	0.539	4.826	0.3933
Curative resection	0.361	0.143	0.914	0.0315

aging studies can easily differentiate ICC from hepatocellular carcinoma and distinguish the macroscopic types of ICC [15,16]. The appearance of periductal-infiltrating ICC is similar to that of perihilar cholangiocarcinoma and the appearance of mass-forming ICC is similar to that of peripheral cholangiocarcinoma [16]. Imaging findings of a widely dilated, ill-defined portal tract or a bile duct with thickened walls continuous with a main tumor showing strong enhancement on delayed-phase computed tomography and peripheral bile duct dilatation suggest that the tumor is a mass-forming plus periductal-infiltrating ICC [17]. We believe that the macroscopic type of ICC should be determined with preoperative imaging studies, and this information is helpful in selecting treatment.

REFERENCES

1. Kawarada Y, Mizumoto R: Cholangiocellular carcinoma of the liver. Am J Surg 1984;147:354–359.
2. Chen MF, Jan YY, Wang CS, et al.: Clinical experience in 20 hepatic resections for peripheral cholangiocarcinoma. Cancer 1989;64:2226–2232.
3. Yamamoto J, Kosuge T, Takayama T, et al.: Surgical treatment of intrahepatic cholangiocarcinoma: Four patients surviving more than five years. Surgery 1992;111:617–622.
4. Yamamoto M, Takasaki K, Tsugita M, et al.: Cholangiocellular carcinoma in a patient who had survived for six years after extended left hepatic lobectomy and caudate lobe resection with pancreatoduodenectomy. J Hep Bil Pancr Surg 1996;3:319–322.
5. Cherqui D, Tantawi B, Alon R, et al.: Intrahepatic cholangiocarcinoma; Results of aggressive surgical management. Arch Surg 1995;130:1073–1078.
6. Nakeeb A, Pitt HA, Sohn TA, et al.: Cholangiocarcinoma: A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996;224:463–475.
7. Liver Cancer Study Group of Japan, editors: Classification of primary liver cancer. Tokyo: Kanehara Shuppan; 1997. Macroscopic typing of intrahepatic cholangiocarcinoma. p. 6–7.
8. Nagorney DM, Donohue JH, Farnell MB, et al.: Outcomes after curative resections of cholangiocarcinoma. Arch Surg 1993;128: 871–879.
9. Washburn WK, Lewis WD, Jenkins RL: Aggressive surgical resection for cholangiocarcinoma. Arch Surg 1995;130:270–276.
10. Cameron JL, Pitt HA, Zinner MJ, et al.: Management of proximal cholangiocarcinoma by surgical resection and radiotherapy. Am J Surg 1990;159:91–98.
11. Chou FF, Sheen-Chen SM, Chen CL, et al.: Prognostic factors of resectable intrahepatic cholangiocarcinoma. J Surg Oncol 1995; 59:40–44.
12. Yasui K, Hirai T, Kato T, et al.: A new macroscopic classification

predicts prognosis for patients with liver metastases from colorectal cancer. Ann Surg 1997;226:582–586.
13. Weinbren K, Mutum SS: Pathological aspects of cholangiocarcinoma. J Pathol 1982;139:217–238.
14. Nakajima T, Kondo Y, Miyazaki M, et al.: A histopathologic study of 102 cases of intrahepatic cholangiocarcinoma: Histologic classification and modes of spreading. Hum Pathol 1988;19:1228–1234.
15. Nesbit GM, Johnson CD, James EM, et al.: Cholangiocarcinoma: Diagnosis and evaluation of resectability by CT and sonography as procedures complementary to cholangiography. Am J Roentgenol 1988;151:933–938.
16. Choi BI, Han JK, Kim TK: Diagnosis and staging of cholangiocarcinomas by computed tomography. In: Meyers MA (ed): Neoplasms of digestive tract. Imaging, staging, and management. Philadelphia: Lippincott-Raven; 1998:508–516.
17. Honda H, Onitsuka H, Yasumori K, et al.: Intrahepatic peripheral cholangiocarcinoma: Two-phased dynamic incremental CT and pathologic correlation. J Comput Assist Tomogr 1993;17:397–402.